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Wheel running exercise attenuates vulnerability to self-administer nicotine in rats

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ABSTRACT

Background: Preventing or postponing tobacco use initiation could greatly reduce the number of tobacco-related deaths. While evidence suggests that exercise is a promising treatment for tobacco addiction, it is not clear whether exercise could prevent initial vulnerability to tobacco use. Thus, using an animal model, we examined whether exercise attenuates vulnerability to the use and reinforcing effects of nicotine, the primary addictive chemical in tobacco.
Methods: Initial vulnerability was assessed using an acquisition procedure wherein exercising (unlocked running wheel, $n = 10$) and sedentary (locked or no wheel, $n = 12$) male adolescent rats had access to nicotine infusions (0.01-mg/kg) during daily 21.5-h sessions beginning on postnatal day 30. Exercise/sedentary sessions (2-h/day) were conducted prior to each of the acquisition sessions. The effects of exercise on nicotine's reinforcing effects were further assessed in separate groups of exercising (unlocked wheel, $n = 7$) and sedentary (no wheel, $n = 5$) rats responding for nicotine under a progressive-ratio schedule with exercise/sedentary sessions (2-h/day) conducted before the daily progressive-ratio sessions.
Results: While high rates of acquisition of nicotine self-administration were observed among both groups of sedentary controls, acquisition was robustly attenuated in the exercise group with only 20% of exercising rats meeting the acquisition criterion within the 16-day testing period as compared to 67% of the sedentary controls. Exercise also decreased progressive-ratio responding for nicotine as compared to baseline and to sedentary controls.
Conclusions: Exercise may effectively prevent the initiation of nicotine use in adolescents by reducing the reinforcing effects of nicotine.

1. Introduction

Early smoking initiation is associated with heavy smoking (Taioli and Wynder, 1991), nicotine dependence (Breslau et al., 1993; Van De Ven et al., 2010), and difficulty quitting later in life (Breslau and Peterson, 1996; Khuder et al., 1999), suggesting that the earlier one begins to smoke, the more likely they will die from smoking-related diseases (Hegmann et al., 1993; McCarron et al., 2001). Although rates of smoking initiation among adolescents have decreased over the years, rates of use remain high among adolescents. The Substance Abuse and Mental Health Services Administration (2014) estimated that in the past year, 3 million adolescents (ages 12–17) smoked cigarettes and each day 3701 adolescents smoked for the first time. In addition, the popularity of electronic cigarettes and hookah has rapidly increased among adolescents resulting in no net change in tobacco and nicotine use among adolescents since 2011 (Arrazola et al., 2015). These statistics indicate that further investigation into potential treatments that prevent the initiation of tobacco and nicotine use in adolescents is needed. In this regard, animal models are useful to identify treatments that prevent the initiation of nicotine self-administration, a model with good predictive validity for tobacco use (O'Dell and Khroyan, 2009).

Clinical and preclinical data suggest that physical activity may protect against the initiation of drug use. Epidemiological studies have consistently demonstrated that adolescents involved in some sort of physical activity are less likely to be current smokers as compared to their less active peers (for a review see Lynch et al., 2013). A

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major confound in this literature is that most physically active teens participate in organized sports. Since some reports have found that participation in specific sports may increase risk for use of smokeless tobacco, alcohol, or other drugs (Aaron et al., 1995; Castrucci et al., 2004; Kirkcaldy et al., 2002; Mattila et al., 2012; Moore and Werch, 2005; Pate et al., 2000; Rainey et al., 1996; Terry-McElrath and O'Malley, 2011; for review see Lisha and Sussman, 2010), it is likely that psychosocial influences associated with being an athlete also affect drug use. However, in prospective studies in adult smokers, acute bouts of exercise have been shown to decrease desire to smoke and cigarette craving (for review see Haasova et al., 2013; Roberts et al., 2012; Taylor et al., 2007) indicating that exercise itself may decrease nicotine use. Further work is necessary to determine if exercise, without confounding social factors, can prevent nicotine use initiation.

Factors that may delay or prevent the initiation of regular drug use in humans can be difficult to determine in prospective studies since it is unethical to expose drug-naïve individuals, particularly adolescents, to drugs. The use of animal models circumvents this issue and, like in humans, many variables have been shown to influence the risk of drug acquisition (Campbell and Carroll, 2000). Acquisition is usually modeled in drug and experimentally naïve animals allowed to respond for drug in operant sessions. In rats, wheel running, a model of aerobic exercise, has been shown to be effective in reducing the acquisition of cocaine and methamphetamine self-administration (Engelmann et al., 2013; Smith and Pitts, 2011), suggesting that there is a biological basis for the effect of exercise in preventing drug use. Furthermore, wheel running has been found to reduce motivation to self-administer cocaine under a progressive ratio (PR) schedule indicating that exercise may prevent drug use initiation by reducing the reinforcing effects of these drug (Smith et al., 2008). However, the efficacy of wheel running exercise in decreasing the acquisition of nicotine self-administration and its reinforcing effects are not yet known. Thus, one goal of this study was to test the hypothesis that voluntary wheel running exercise would prevent the initiation of nicotine self-administration in adolescent rats. A second goal of this study was to determine if exercise decreases the reinforcing efficacy of nicotine, as has been observed with other drugs of abuse. To address these goals, drug naïve adolescent rats were permitted daily bouts of wheel running exercise followed by nicotine self-administration sessions under acquisition testing conditions or PR testing conditions in rats that had previously acquired nicotine self-administration.

2. Methods

2.1. Animals

Male Sprague-Dawley (Charles River Laboratories, Portage, ME, USA) rats ($N = 34$; experiment 1, $n = 22$; experiment 2, $n = 12$) were shipped on day of weaning (postnatal day 21) and arrived at the laboratory on postnatal day 22. Upon arrival, animals were individually housed in self-administration chambers, and were maintained on a 12-h light/dark (house lights on at 0700) cycle with *ad libitum* access to water and food except during exercise sessions during which only water was available. Animals were habituated in chambers for 3–4 days prior to any training and 6 days prior to surgery. All procedures were approved by The Animal Care and Use Committee at the University of Virginia and were in accordance with the guidelines set by the National Institutes of Health.

2.2. Apparatus

Individual 31 cm × 24 cm × 21 cm self-administration chambers (ENV-008CT, Med Associates, St. Albans, VT, USA) were equipped with a house light (4.76 W), water bottle holder, food-hopper, retractable active (drug-associated) lever, a cue light (4.74 W) above the active lever, and a stationary inactive lever. Each chamber was centered within a ventilated sound-attenuating box (ENV-018M, Med Associates, St. Albans, VT, USA) along with a pump (PHM-100, Med Associates, St. Albans, VT, USA). A 10-ml drug syringe was mounted on the pump and connected to Tygon tubing that attached to swivel (Instech Laboratories Inc., Plymouth Meeting, PA, USA) embedded in a counterbalanced metal arm above the chamber. A polyethylene tube encased in a metal spring (C313CS; PlasticsOne, Roanoke, VA, USA) was attached to the swivel and to a 22-gauge guide (C313G; PlasticsOne, Roanoke, VA, USA) embedded within an infusion harness (CIH95AB; Instech Laboratories Inc., Plymouth Meeting, PA, USA) the animal wore following surgery and thereafter until study completion. The house light was illuminated from 0700 to 1900 daily to maintain a 12-h light dark cycle. Running wheels (ENV-046; Med Associates, St. Albans, VT, USA) with polycarbonate cage attachment were equipped with a revolutions counter.

2.3. Surgery

On postnatal day 28, rats underwent surgery to implant a chronic indwelling silastic catheter (0.51 and 0.94 mm o.d.; Dow Corning Corporation) into the right jugular vein as described previously (Lynch, 2008). Rats were given ketoprofen (2–5 mg/kg, subcutaneous) and gentamicin (5.5 mg/kg, i.v.) on the day of surgery and for 2 subsequent days. Rats were given 2 days to recover from surgery prior to nicotine self-administration testing. Catheter patency was assessed by flushing a small amount of heparinized saline into the catheter and pulling back to check for the presence of blood. This check was conducted for 2 days following surgery and thereafter every Monday, Wednesday, and Friday prior to self-administration sessions.

2.4. Drug

Nicotine bitartrate (Sigma–Aldrich, St. Louis, MO, USA) was dissolved in 0.9% sterile saline (pH 7.4) and passed through a microfilter with dose expressed as the free base weight. A single moderate dose (10 μg/kg/infusion) of nicotine was selected based on previous work demonstrating this dose leads to rapid and high rates of acquisition of nicotine self-administration in adolescent males (Lynch, 2009). Infusions were delivered at a rate of 0.1 ml/s and infusion volume was adjusted for animal's weight. Nicotine solution was stored in the dark at 4 °C but was available at room temperature during self-administration.

2.5. Experiment 1: acquisition study

Rats were randomly assigned to either an exercise ($n = 10$) or control condition ($n = 12$). Controls included a group that did not have access to a wheel (no wheel; $n = 6$) and as a control for environmental enrichment, a group that had access to a running wheel that was stationary (locked wheel; $n = 6$). Prior to surgery, on postnatal days 23–24, rats were acclimated to their assigned wheel condition for 2 h each day (0930–1130). Beginning on postnatal day 30, rats were moved from their self-administration chambers to their assigned wheel condition. During the 2-h access session, both wheel groups could move freely between the wheel and the polycarbonate cage. Rats were then moved back to their self-administration chambers at 1130. Daily nicotine self-administration sessions began at noon with the presentation of the active lever into the chamber. Responses on the active lever during each session were reinforced under a fixed ratio (FR) 1 schedule and each infusion was paired with the illumination of a cue light above the active lever. Sessions were terminated when the rat obtained all 20 infusions that were available or after 21.5 h. Acquisition was defined as 2 consecutive days of 20 infusions with a 2:1 preference of the active lever over the inactive lever. Fig. 1 outlines the experimental timeline.

2.6. Experiment 2: progressive ratio study

In this experiment, rapid acquisition of nicotine self-administration was desired and therefore a separate cohort of male adolescent rats ($n = 12$) were food pretrained to lever press for sucrose pellets under an FR1 schedule until 2 consecutive days of 50 pellet deliveries as described previously (Sanchez et al., 2013a,b). Rats then underwent surgery on postnatal day 28 as described above. Beginning on postnatal day 30, rats were trained to self-administer nicotine under an FR1 schedule with a maximum of 20 deliveries each day for 5 days. Acquisition of nicotine self-administration was defined as 2 consecutive days of receiving all 20 infusions with at least a 2:1 preference for the active lever over the inactive lever. All rats reached acquisition criteria within 5 days, at which point they were randomly assigned to exercise ($n = 7$) or sedentary ($n = 5$) conditions. In this experiment, the sedentary controls were not exposed to a running wheel since our previous experiment did not reveal a significant effect of exposure to a locked running wheel (see Fig. 3). Following acquisition, rats began a PR schedule of reinforcement for nicotine infusions. Under this schedule the lever response requirement increases (i.e., 1, 2, 4, 6, 9, 12, 15, 20, 25, 32, etc.) for each subsequent infusion. The final ratio completed, or the breakpoint, is thought to be a sensitive measure of reinforcing efficacy or motivation for the drug (Arnold and Roberts, 1997). Breakpoints were recorded after each session, and were typically reached approximately 2 h after the start of the session. A stable baseline of PR responding was defined as no increasing or decreasing trends in breakpoints for 3 consecutive sessions. All rats reached stable responding on PR schedule quickly, within 3–4 days, and rates did not differ between groups. Once a stable baseline was reached, rats were given 2-h access to their exercise condition before PR sessions for 5 consecutive